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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/706,877	11/12/2003	Stuart L. Schreiber	42697.137 (US8)	5816

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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	**PAPER NUMBER**
1617	

NOTIFICATION DATE	DELIVERY MODE
09/25/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/706,877	SCHREIBER ET AL.	
	Examiner	Art Unit	
	Umamaheswari Ramachandran	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner notes the receipt of the amendments and remarks, Rule 130, 131, 132 Affidavits received in the office on 6/21/2007. Claims 2-10 are pending and are being examined on the merits herein.

Response to Remarks

Applicant's arguments filed 6/21/2007 regarding the objection to Specification is found to be persuasive and is withdrawn. Applicant's arguments filed 6/21/2007 regarding the rejection of claim 2 under 35 U.S.C. 112, second paragraph is found to be persuasive and is withdrawn. Applicant's arguments filed 6/21/2007 regarding the rejection of claims 2, 5-10 under 35 U.S.C. 112, first paragraph, is found to be persuasive and is withdrawn. Applicant's arguments filed 6/21/2007 regarding the rejection of claims 2-5, 9 and 10 under 35 U.S.C. 102(a) as being anticipated by Fenteany et al (PNAS, Vol. 91, pp 3358-3362) is found to be persuasive and is withdrawn. Applicant's arguments filed 6/21/2007 regarding the rejection of claims 2-10 under 35 U.S.C. 112, first paragraph have been fully considered but they are not persuasive. Accordingly, the rejections of the claims 2-10 are being maintained and is given below for Applicants' convenience. The Office Action is made Final.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cell cycle analysis with lactacystin does not reasonably provide enablement for the treatment of all types of cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The nature of the Invention:

The rejected claims are drawn to a method of treating cancer comprising administering a compound of formula listed in claim 2.

(2) Breadth of the claims:

Claims 2, 3 and 4 are broad as they drawn to a method of treating various types of cancer comprising administering a compound of formula listed in claim 2. The

complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

(3) Guidance of the Specification:

The guidance given by the specification for treating various types of cancer comprising administering a compound of formula listed in claim 2 is none. No examples are provided for treating various types of cancer comprising administering a compound of formula listed in claim 2. The only example provided is the cell cycle analysis with lactacystin and no examples are provided for any of the lactacystin analogs including the species elected.

The specification does not provide any relationship to how the cell cycle analysis could be useful for the treatment of cancer.

(4) Working Examples:

The specification does not provide any examples for treating various types of cancer comprising administering a compound of formula listed in claim 2. The only example provided is the cell cycle analysis with lactacystin and no examples are provided for any of the lactacystin analogs including the species elected.

(5) The relative skill of those in the art:

The relative skill of those in the medical treatment art is high, requiring advanced education and training.

(6) The predictability of art:

Claims 2, 3 and 4 are directed to a method of treating various types of cancer comprising administering a compound of formula listed in claim 2. The claims are so

broad and there is a high degree of unpredictability involved. Despite the advanced training in the medical treatment arts, the arts are highly unpredictable.

(7) The Quantity of Experimentation Necessary:

In order to practice the above claimed invention, one of skill in the art would have to first envision formulation, dosage, duration, route and, in the case of human treatment, an appropriate animal model system to test the lactacystin analog compound of formula listed in claim 2, to determine whether or not they are useful in the treatment of every type of cancer listed in claim 4. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regarding the treatment of various types of cancers by lactacystin analog compound of formula listed in claim 2, one of skill in the art would have to envision a modification in the formulation, dosage, duration, route of administration etc. and appropriate animal model system, or envision an entirely new combination of the above and test the system again. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention of treating various types of cancers comprising administering a compound of formula listed in claim 2. Applicant fails to provide information sufficient to practice the claimed invention, absent undue experimentation. Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Response to Arguments

Applicant's arguments regarding the rejection of claims 2-10 under 35 U.S.C. 112, first paragraph have been fully considered but they are not persuasive. Applicants' argue that it would not require undue, unpredictable experimentation to practice the claimed invention. In response, as Applicants have admitted that the specification discloses methods for testing the compounds (four, Table 3) of formula (claim 2) for biological activity against MG-63 osteosarcoma cells and Neuro 2A neuroblastoma cells. The specification teaches that "Biological activity of compound refers to the ability of the compound to induce neurite outgrowth in Neuro 2A neuroblastoma cells and to inhibit cell cycle progression in MG-63 osteosarcoma cells (p 89, Example 5). Applicants' have shown only what the prior art Fenteany et al (Proc Natl Acad Sci. Vol. 91, p 3358-62, Apr 12 1994) teaches. Fenteany teach clasto lactacystin β-lactone, the elected species induces neurite outgrowth in Neuro 2A neuroblastoma cells and to inhibit cell cycle progression in MG-63 osteosarcoma cells. Applicants' have not shown any data administering the compounds to a subject in the treatment of cancer. The specification do not provide any experimental data showing the effectiveness of the compound in the treatment of cancer. The lack of working examples is a critical and crucial factor to be considered in the treatment of a disease. Applicant has provided no in vivo data or actual case studies administering to a subject a compound of formula in claim 2 in a method of treatment of cancer as claimed. Despite the advanced training of the ordinary practitioners in the pharmaceutical development and medical treatment arts, the arts are highly unpredictable. The state of

the art is such that it is not possible to predict the activity of a compound, whether in vitro or in vivo, based on the structure alone or based on the mechanism. Applicants' claim that the compounds of formula 2 block the action of proteasome in vitro and hence they treat cancer. A large problem with going from in vitro data to in vivo efficacy is the bioavailability or specificity of a compound. Typically, for the development of a method of treating a disease, a certain pharmacological property of a compound, such as receptor binding or activation, or cytotoxicity, must be tested or verified in an in vitro model. In order to predict the in vivo activity of a compound based on the in vitro assay, the assay itself must be definitively well correlated to the pathophysiology of a target disease and verified as being predictive of the in vivo activity of a compound. For example, if a receptor is known to be overactivated in the pathophysiology of a disease, the ordinary practitioner would predict that a compound that inhibits the activation of the receptor may be useful for the treatment of said disease. However, even for in vitro models that involve receptors known to be involved in the pathophysiology of a disease, translating the in vitro efficacy of a compound to in vivo efficacy for the treatment of a disease is notoriously unpredictable unless the correlation has been conclusively verified. Further, the in vivo efficacy of a compound is not only determined by the affinity or activity of the compound on its target receptor in a validated in vitro assay, but by a range of other factors including the bioavailability of the compound, its pharmacokinetic profile, and the specificity of the compound for the desired target versus other potential targets. Applicant has only shown data of the biological activity against MG-63 osteosarcoma cells and Neuro 2A neuroblastoma cells, blocking the

action of proteasome in vitro. The claims are directed to a method of treating cancer comprising administering to a subject an effective anti-cancer amount of a pharmaceutical composition of formula claimed in claim 2. Based on the functionality and mechanism that the claimed species can inhibit proteasomes in vitro does not really provide evidence that the claimed species can treat cancer. The central question is a compound that has been shown to block the action of proteasome if administered to a live human would have the same effect and effectively treat cancer. Applicant has provided no data to support the claims and assertions that the compounds of formula in claim 2 is administered to patients with cancer and had therapeutic benefits. One of ordinary skill in the art would have to determine the compounds that have been shown to block proteasomes could be used to treat cancer in vivo. Therefore, this determination, which would be required to enable the instantly claimed methods, is considered undue experimentation. Finally, in order to practice the instantly claimed methods, the ordinary skilled artisan would need to determine that for every type of cancer listed in claims 3 and 4 and this would also be considered undue experimentation. Applicants have shown in vitro data only with MG-63 osteosarcoma cells in the inhibition of cell cycle progression. A person of ordinary skill in the art have to conduct experiments in vitro with different cell lines for types of cancer listed in claim 4 and then translate the in vitro efficacy to in vivo efficacy and then determine other parameters such as specificity, bioavailability etc in order to use the compounds in a method of treatment of different types of cancer. Thus, the instantly claimed methods of treating cancer or any type of cancer listed in claim 4, comprising administering to a

subject an effective amount of the pharmaceutical composition of formula of claim 2 are not enabled. Thus, the rejection under 35 USC § 112, first paragraph, is properly maintained.

Conclusion

No claims are allowed.

The rejection is maintained and is given in the Office Action for Applicants' convenience. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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